Supplementary information: Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study

1. Supplementary Document 1: Study CRF
2. Supplementary Figure 1: Difference between pre-initiation and post-initiation delta lung function in restricted analysis (N=64).
3. Supplementary Figure 2: Difference in change in lung function according to patient sex (N=123)
4. Supplementary Figure 3: Difference between pre-initiation and post-initiation delta lung function in restricted analysis according to subgroups (N=64).
5. Supplementary Figure 4: Lung function change according to nintedanib dose reduction (N=123)
6. Supplementary Figure 5: Timeline figure showing the data collection used for the study analysis at each visit
7. Supplementary Table 1: Complete clinical data
8. Supplementary Table 2: Rate of Lung function change pre and post-nintedanib, with difference overall and by subgroup (N=123)
9. Supplementary Table 3: Sensitivity analyses of rate of ppFVC change per year (N=122)
10. Supplementary Table 4: Lung function according to changes in nintedanib dose (N=72)
11. Supplementary Table 5: Lung function according to changes in concurrent immunosuppression (N=72)

Supplementary Table 1: Complete clinical data

	Time point	N=126	%
FVC			
	Pre-nintedanib	113	89.7%
	Treatment initiation	103	81.7%
	Post-nintedanib	84	66.7%
ppFVC			
	Pre-nintedanib	112	88.9%
	Treatment initiation	102	81.0%
	Post-nintedanib	85	67.5%
ppDLCO			
	Pre-nintedanib	104	82.5%
	Treatment initiation	79	62.7%
	Post-nintedanib	68	54.0%
ppKCO			
	Pre-nintedanib	95	75.4%
	Treatment initiation	74	58.7%
	Post-nintedanib	65	51.6%
Shortness of breath			
	Treatment initiation	113	89.7%
	Post-nintedanib	103	81.7%
Cough			
	Treatment initiation	78	61.9%
	Post-nintedanib	78	61.9%
Exercise tolerance			
	Treatment initiation	112	88.9%
	Post-nintedanib	101	80.2%

Complete data available for each of the above fields at the various points

Supplementary Table 2. Rate of Lung function change pre and post-nintedanib, with difference overall and by subgroup (N=123)

	n	Rate pre	95%CI	Rate post	95%CI	Difference	95%CI	p
FVC (ml)								
Overall	123	-239.86	-292.71 to -187.01	-88.79	-156.23 to -21.34	151.23	47.45; 255.01	0.004
Diagnosis								
fHP	42	-232.8	-313.8 to -151.8	-109.8	-219.6 to 0.05	125.4	-18.4 to 269.1	0.087
CTD-ILD	44	-190.8	-276.0 to -105.7	-66.3	-179.1 to 46.4	122.5	-47.7 to 292.7	0.158
Other	37	-281.1	-391.0 to -171.2	-113.1	-243.6 to 17.4	172.7	-25.8 to 371.2	0.088
CT pattern								
UIP	29	-246.3	-370.1 to -122.5	-120.6	-271.5 to 30.3	123.8	-94.3 to 342.0	0.266
Non-UIP	93	-225.5	-279.8 to -171.2	-87.1	-162.5 to -11.8	138.1	30.7 to 245.4	0.012
Sex								
Male	57	-295.9	-379.1 to -212.6	-100.7	-198.4 to -2.9	193.4	27.2 to 359.6	0.023
Female	66	-168.3	-215.3 to -121.4	-90.2	-180.7 to 0.3	79.9	-16.0 to 175.8	0.102
ppDLco (%)								
Overall	114	-6.06	-7.35 to -4.77	-2.13	-4.06 to -0.20	3.93	1.27 to 6.60	0.004
Diagnosis								
fHP	39	-7.5	-9.3 to -5.6	-2.5	-5.7 to 0.6	5	1.1 to 8.9	0.013
CTD-ILD	42	-3.9	-5.9 to -1.9	-3.3	-6.4 to -0.3	0.6	-3.9 to 5.1	0.803
Other	33	-6.7	-9.2 to -4.2	-0.1	-4.4 to 4.2	6.6	1.9 to 11.4	0.006
CT pattern								
UIP	27	-6.5	-8.8 to -4.2	-3.8	-7.7 to 0.2	2.6	-2.5 to 7.7	0.312
Non-UIP	86	-5.8	-7.2 to -4.3	-1.7	-3.9 to 0.5	4	1.0 to 7.1	0.009
Sex								
Male	53	-7.2	-8.9 to -5.4	-3.8	-6.4 to -1.1	3.4	-0.6 to 7.3	0.092
Female	61	-4.6	-6.3 to -3.0	-0.6	-3.2 to 2.0	4	0.8 to 7.2	0.014
Kco (%)								
Overall	108	-5.7	-8.36 to -3.04	-1.26	-5.18 to -2.65	4.43	-0.99 to 9.86	0.109
Diagnosis								
fHP	38	-8.6	-13.3 to -4.0	0.2	-6.4 to 6.7	9	-0.8 to 18.7	0.071
CTD-ILD	39	-4.4	-10.2 to 1.5	-2.1	-8.35 to 4.1	2.3	-8.2 to 12.8	0.666
Other	31	-4.2	-8.4 to 0.1	-2.9	-11.9 to 6.1	1.3	-6.3 to 8.9	0.732
CT pattern								
UIP	25	-6.5	-11.2 to -1.7	1.4	-6.7 to 9.4	8.1	-2.2 to 18.3	0.122
Non-UIP	82	-5.5	-8.7 to -2.3	-2.2	-6.8 to 2.3	3.3	-3.1 to 9.9	0.314
Sex								
Male	51	-7.3	-11.2 to -3.4	-5.4	-10.8 to 0.02	1.9	-6.1 to 9.9	0.647
Female	57	-4	-7.5 to -0.5	2.35	-2.9 to 7.6	6.2	-0.7 to 13.2	0.079

Rate of lung function change estimated from longitudinal multilevel models for repeat measures adjusted for age, sex, diagnostic group, radiologic pattern and early cessation of treatment (<12 months). Difference between groups estimated with restricted linear spline include knot at initiation.

Supplementary Table 3. Sensitivity analyses of rate of ppFVC change per year (N=122)

Sensitivity analysis	Rate pre %	95%CI	Rate post %	95%CI	Difference %	95%CI	p
ppFVC							
1. Overall	-6.91	-8.45 to -5.36	-2.57	-4.59 to -0.54	4.34	1.35 to 7.33	0.004
2. Time continuous/yr	-6.63	-8.47 to -4.79	-2.96	-5.18 to -0.74	3.67	0.32 to 7.02	0.032
3. Imputation I	-6.02	-8.27 to -3.77	-3.35	-5.68 to -1.03	2.67	-1.28 to 6.61	0.185
4. Imputation II	-5.25	-6.73 to -3.77	-2.75	-4.23 to 1.27	2.50	-0.07 to 5.06	0.057
5. Imputation III	-6.86	-8.29 to -5.42	-3.84	-5.27 to -2.40	3.02	0.72 to 5.32	0.010

1. Overall analysis: identical to primary analysis with use of percent predicted FVC as outcome.
2. Time continuous: timing of ppFVC record from nintedanib initiation modelled as continuous variable rather than discrete time point.
3. Imputation I: missing ppFVC imputed at cohort median per time point (pre, initiation, post).
4. Imputation II: missing ppFVC imputed as carried backward or forward from non-missing time point.
5. Imputation III: missing ppFVC imputed at 10% relative decline from pre-nintedanib to initiation and initiation to post-nintedanib.

Supplementary Table 4. Lung function according to changes in nintedanib dose

Nintedanib dose	Change FVC (%) post-nintedanib				Difference in FVC change pre vs post nintedanib			
	n	mean	SD	p	n	mean	SD	p
Maintained	51	-3.69	7.77		46	2.09	11.38	
Reduced	21	-0.80	7.60	0.154	17	4.91	8.51	0.357
	Change in DLco(%) post-nintedanib				Difference in DLco change pre vs post-nintedanib			
	n	mean	SD	p	n	mean	SD	p
Maintained	38	-2.89	6.49		33	3.53	8.07	
Reduced	16	-1.53	4.94	0.456	13	1.38	8.98	0.436
	Change in Kco(%) post-nintedanib				Difference in Kco change pre vs post-nintedanib			
	n	mean	SD	p	n	mean	SD	p
Maintained	36	-0.88	13.91		31	6.13	18.53	
Reduced	15	-4.16	7.66	0.395	10	-3.71	14.13	0.133

Supplementary Table 5. Lung function according to changes in concurrent immunosuppression

	Change FVC (%) post-nintedanib				Difference in FVC change pre vs post nintedanib			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	9	-4.19	9.93		9	-0.60	11.45	
Maintained	40	-3.55	7.57		32	1.89	11.05	
Reduced	23	-1.11	7.30	0.425	22	5.66	9.61	0.261
	Change in DLco(%) post-nintedanib				Difference in DLco change pre vs post-nintedanib			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	6	-1.45	7.29		6	4.70	11.25	
Maintained	31	-3.15	6.30		24	0.25	5.68	
Reduced	17	-1.63	5.35	0.652	16	6.27	9.49	0.065
	Change in Kco(%) post-nintedanib				Difference in Kco change pre vs post-nintedanib			
	N	mean	SD	p	n	mean	SD	p
Immunosuppressant dose								
Increased	6	5.08	16.06		6	10.53	26.43	
Maintained	28	-2.31	12.66		21	1.60	16.84	
Reduced	17	-3.52	10.46	0.337	14	4.02	15.91	0.570